Resistant and sensible cancerous networks: differences and therapeutic strategies

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Context

The SyMeTRIC project

A regional project for developing systems medicine:

1. integrating various information sources
2. developing analysis and modeling tools
3. accessible from the web
4. building bio-pathological models
5. predicting the good treatment for the right patient

Project leaders:

- Jéremie Bourdon (LS2N)
- Richard Redon (Institut du Thorax)

Project coordinator:

- Alban Gaignard (CHU de Nantes)

A pluridisciplinary problematic I

Biological side

- problem: cancer (obvious)
- solution: chemotherapy (among others)
- problem: heavily toxic
- solution: targeted therapy
- problem: resistance (loss of efficacy)
- solution: therapeutic targets against resistance

A pluridisciplinary problematic II

Computational side

- problem: large amount of omics data
  - how to interpret them?
  - how to extract knowledge?
- solution: mechanistic modeling
  - model the mechanisms
  - knowledge: model's structure
  - data: model's state
  - simulations
    $\Rightarrow$ prediction of new knowledge

Resources I

Biological resources

- cancerous cells:
  - multiple myeloma: 37 cell lines
  - breast cancer: 36 tumor samples
  - sensible and resistant to several treatments:
- per cell line and per treatment:
  - GEP (gene expression profile)
  - phenotype: cell death

Online resources: signaling pathway repository

KEGG (Kanehisa *et al* Nucleic Acids Res 2017), chosen for:

- its reliability
- its exportation format (KGML)
- its API

Resources II

Computational resources

1. network reconstruction:
   - MCWalk (Kittas *et al* FEBS J 2016)
   - connect genes according to a reference network
     $\Rightarrow$ genes + KEGG + MCWalk = reconstructed network
2. consistency, repair and coloration:
   - iggy (Thiele *et al* BMC Bioinformatics 2015)
3. predictions: signatures and therapeutic targets
   - logical programming (ASP): to develop
   - Boolean and multivalued:
     - kali (Poret *et al* C R Biol 2014)
     - assuming that attractor = phenotype
     - 2 versions of the network: desirable and undesirable
       $\Rightarrow$ reduce undesired attractors' reachability
       $\Rightarrow$ therapeutic targets against the undesirable

Strategy (per cancer) I

Reconstructing the network regulating the GEP

1. selecting the genes:
   - outputs of an gene expression regulation (GErel in KEGG)
   - belonging to the GEP
2. Reconstructing the network regulating the expression of these genes:
   - GErel outputs + KEGG + MCWalk

Coloring the network explaining the GEP

1. discretizing the GEP:
   - Boolean: median
   - multivalued: quartiles
2. coloring the network:
   - network + discretized GEP + iggy

Strategy (per cancer) II

Predicting therapeutic targets against resistance

- logical programming (ASP):
  1. finding signatures in pathways:
     - resistant
     - sensible

     $\Rightarrow$ compare to identify resistance's mechanisms
  2. finding resensitizing therapeutic interventions

     $\Rightarrow$ therapeutic targets against resistance
- Boolean/multivalued:
  1. network to logical equations (AND, OR, NOT)

     $\Rightarrow$ modeling the interactions
  2. selecting a sensible network
  3. selecting a resistant network
  4. running kali
  5. assessing the obtained therapeutic target combinations
- testing *in vitro* the predicted therapeutic targets

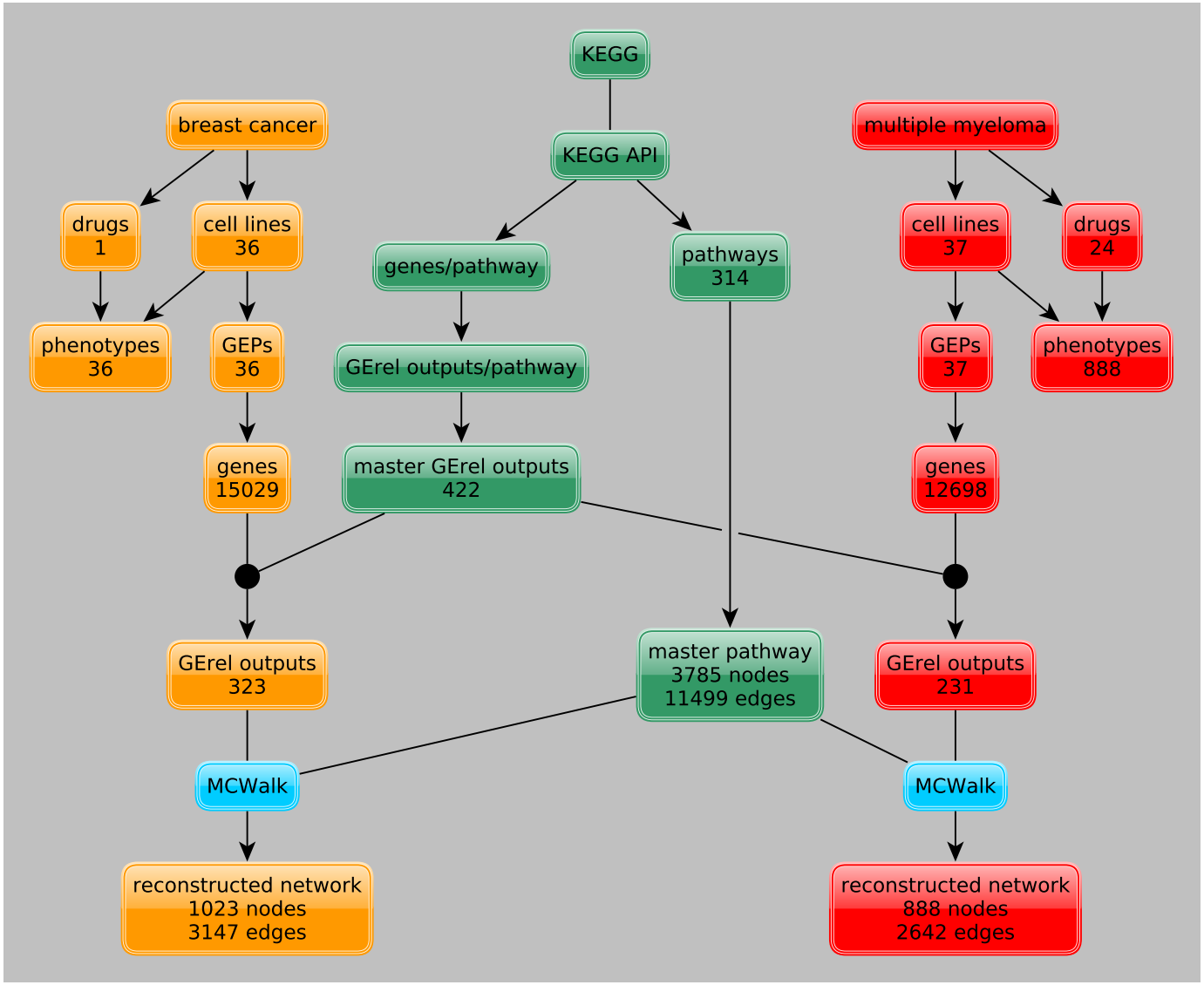
Results I

Interactions in KEGG

- fall into 4 classes:
  - ECrel: enzyme – enzyme
  - GErel: transcription factor – gene
  - PCrel: protein – compound
  - PPrel: protein – protein
- considered for modeling:
  - activation
  - inhibition
  - expression
  - repression
  - binding/association
  - dissociation
- added:
  - is member

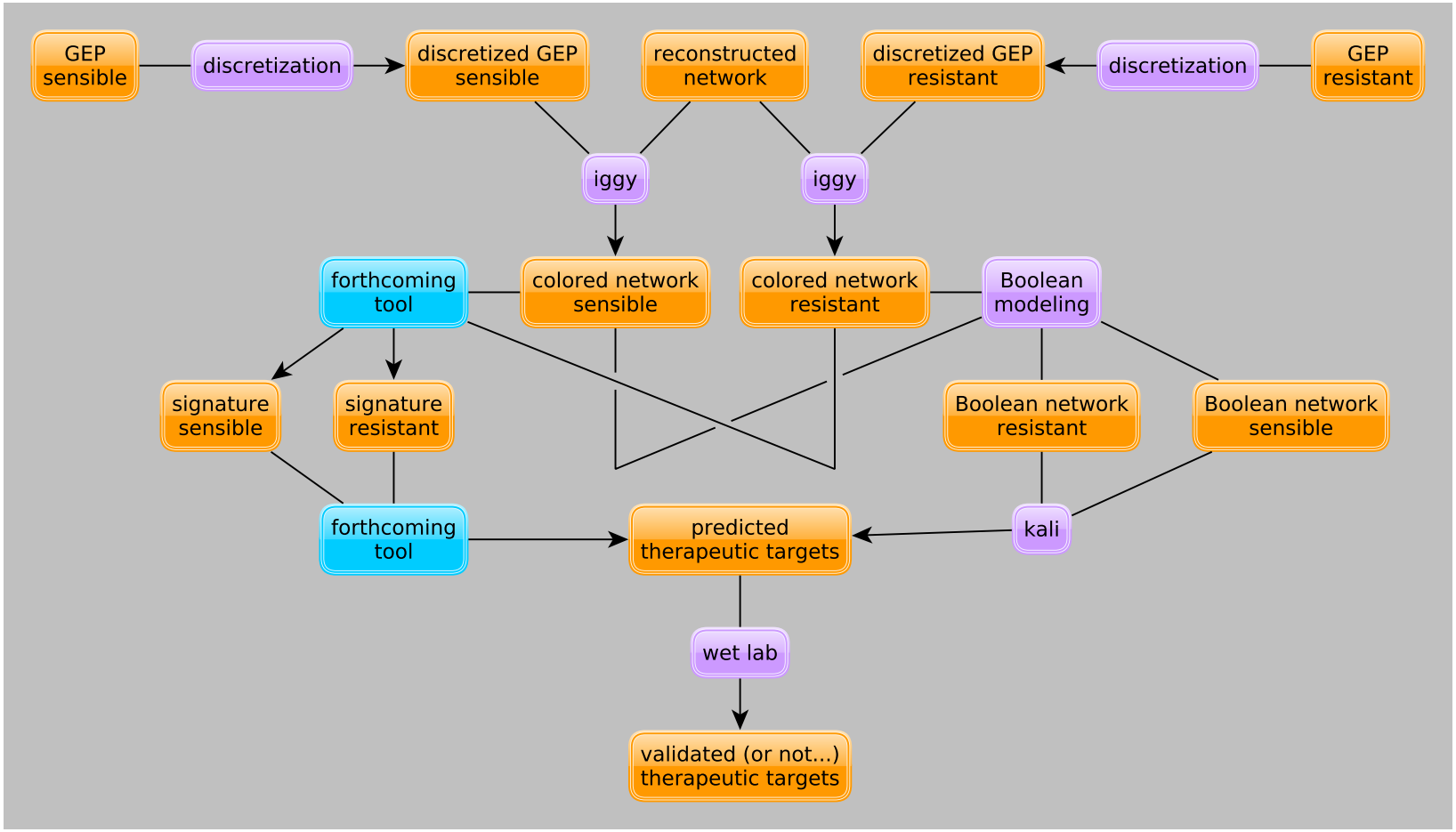
Results II

Obtained:



Results III

Perspectives:



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  - network reconstruction
  - network coloration
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  - network reconstruction
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  - signaling pathway repositories
  - network reconstruction

A little bit of KGML

```
<?xml version="1.0"?>
<!DOCTYPE pathway SYSTEM "http://www.kegg.jp/kegg/xml/KGML_v0.7.2_.dtd">
<!-- Creation date: Feb 24, 2016 14:39:53 +0900 (GMT+9) -->
<pathway name="path:hsa04012" org="hsa" number="04012"
        title="ErbB signaling pathway"
        image="http://www.kegg.jp/kegg/pathway/hsa/hsa04012.png"
        link="http://www.kegg.jp/kegg-bin/show_pathway?hsa04012">
    <entry id="67" name="hsa:1950" type="gene"
        link="http://www.kegg.jp/dbget-bin/www_bget?hsa:1950">
        <graphics name="EGF, HOMG4, URG" fgcolor="#000000" bgcolor="#BFFFBF"
            type="rectangle" x="69" y="217" width="46" height="17"/>
    </entry>
    <entry id="75" name="undefined" type="group">
        <graphics fgcolor="#000000" bgcolor="#FFFFFF"
            type="rectangle" x="200" y="208" width="46" height="34"/>
        <component id="14"/>
        <component id="60"/>
    </entry>
    <relation entry1="78" entry2="46" type="PPrel">
        <subtype name="activation" value="--&gt;"/>
        <subtype name="phosphorylation" value="+p"/>
    </relation>
</pathway>
```